UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,918	12/28/2001	Rajiv Shah	047711-0293	2208

7590 11/01/2006

Irvin C. Harrington, III
FOLEY & LARDNER
35th Floor
2029 Century Park East
Los Angeles, CA 90067-3021

EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,918	SHAH ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-46 and 48-54* is/are pending in the application.

4a) Of the above claim(s) *25-43 and 48-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-24 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on August 8, 2006, amending claims 1, 3, 19 and 44 and canceling claim 47, has been entered.

Claims 1, 3-8, 10-46 and 48-54 are pending. Claims 25-43 and 48-54 are withdrawn. Claims 1, 3-8, 10-24 and 44-46 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on August 8, 2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 3-8, 10-24 and 44-47 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "determining whether the colonies contain active glucose oxidase comprises: detecting a concentration of active glucose oxidase". It is

not clear to the Examiner how the concentration of only active glucose oxidase is detected. Further, it is not clear how a concentration of glucose oxidase is detected from the colonies unless the glucose oxidase is first isolated. Therefore, the claim lacks essential steps: isolation step and detecting concentration of only active glucose oxidase. Examiner requests clarification of the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-8, 10-24 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Stemmer, Hatzinikolaou et al., Wagner et al. and Aldrich Catalog.

Claims 1, 3-8, 10-24 and 44-46 are drawn to a method of formulating or producing mutant glucose oxidases by obtaining a library of glucose oxidase genes, creating a library of mutated glucose oxidase genes by the methods recited in claims 20-24, introducing each mutated glucose oxidase genes into separate expression vectors, inserting said vectors into a microorganism recited in claim 19, growing colonies of the microorganism, determining whether the colonies contain active glucose oxidase by determining whether the colonies contain active glucose oxidase by testing glucose oxidase in sensors and using fluorescence of a leuco-cryalsta-violet, and determining whether the colonies are resistant to peroxide.

Valdes et al. (cited previously on form PTO-892) discloses that glucose oxidase in glucose sensors are degraded by peroxide and this "decay can lead to the eventual failure of the senor" (abstract and page 367). Valdes et al. teaches that to ensure longer sensor functionality, instead of replacing the sensor with fresh enzyme, as has been practiced in the art, techniques to "prevent the degradation of the enzyme" is advantageous (page 375). With this teaching at hand, one having ordinary skill in the art would conclude that glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are

known in the art, as discussed below. Valdes et al. also teaches a method of determining activity of glucose oxidase (page 370.

The difference between the reference of Valdes et al. and the instant invention is that the reference of Valdes et al. does not teach a method of producing mutant glucose oxidase that is resistant to degradation from peroxide and detecting concentration of active glucose oxidase in sensors and using fluorescence. However, there are many methods widely available in the art of creating mutant genes by random mutations and screening for mutants displaying desired functional properties, such as having resistance to a chemical, such as a peroxide.

Stemmer (US Patent 6,117,679 – cited previously on form PTO-892) discloses a method of producing mutant enzymes by obtaining a library of genes of interest, creating a library of mutated genes by multiple cycles (at least 2-6 cycles) of PCR, error-prone PCR and/or gene shuffling (abstract, Column 4-11 and Column 22). In the method of Stemmer, each mutated genes are introduced into separate expression vectors, which are then inserted into *E. coli* (Column 25, 31-32). Stemmer teaches these host cells are then tested for the presence of desired mutations, such as growing the cells or colony under selective pressure and isolating the protein and testing of the protein encoded for activity (Column 32). Stemmer teaches a method of screening for colonies having resistance to a chemical by plating transformed cells comprising mutated genes onto agar plates having varying concentrations of said chemical (Column 78).

Hatzinikolaou et al. (cited previously on form PTO-892) discloses a library of glucose oxidase genes known in the art, such as *A. Niger* (page 371). Hatzinikolaou et al. also discloses a method of isolating and purifying glucose oxidase as recited in claims 14-18 and methods of measuring glucose oxidase activity and concentration of glucose oxidase (pages 372-373).

Wagner (EP 0 251 475 A1 - cited previously on form PTO-892) discloses a method of determining glucose oxidase activity via a sensor by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission (pages 2-3). In the method of Wagner, the glucose oxidase is conjugated to a dye and immobilized in the sensor (page 3). Wagner also teaches that any fluorescent dye sensitive to quenching of its fluorescence emission by oxygen can be used (page 5). Leuco-crystal-violet dyes are common fluouresent dyes, (page 1005 Aldrich Catalog - cited previously on form PTO-892).

Therefore, combining the teachings of Valdes et al., Stemmer, Hatzinikolaou et al., Wagner et al. and Aldrich Catalog, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to formulate or produce mutant glucose oxidases having resistance to peroxide by generating a library of mutated genes using the glucose oxidase gene of Hatzinikolaou et al. and the method of Stemmer, transforming *E. coli* with vectors comprising each of the mutated genes, growing colonies of said cells and determining whether the colonies have active glucose oxidase and then determining whether the colonies or the glucose oxidase comprised in the colony are resistant to peroxide, by using the method of Wagner to

ascertain activity of the glucose oxidase, wherein glucose oxidase is isolated and purified by the method taught by Hatzinikolaou et al. One of ordinary skill in the art would have been motivated to do so in order to generate active glucose oxidases that are resistant to peroxide. One of ordinary skill in the art would have been motivated to produce mutant peroxide resistant glucose oxidases in order to use them in glucose sensors, thereby prolonging their use, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide, leading to failure of the sensor. One of ordinary skill in the art would have had a reasonable expectation of success since Hatzinikolaou et al. teaches glucose oxidase genes, Stemmer teaches a method of generating a library of mutant genes and screening for activity and other desired properties, such as resistance to a chemical, and Wagner teaches how to determine activity of glucose oxidase by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission.

Therefore, the above references render claims 1, 3-8, 10-24 and 44-46 *prima facie* obvious.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that Examiner acknowledges that Valdes et al. do not teach a method of producing mutant glucose oxidase that is resistant to degradation from peroxide, but that Valdes et al. teaches a different procedure, wherein chemical agents are used to address peroxide degradation. While it is true that Valdes et al. do not

teach a method of producing a library of mutated glucose oxidase genes, Valdes et al. does teach that another option of addressing the peroxide degradation of glucose oxidase is to "prevent the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph). With this teaching at hand, one having ordinary skill in the art would conclude that glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use other "techniques", generating glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as taught by Stemmer et al.

Applicants also argue that none of the reference describe or suggests formulating a glucose oxidase enzyme by "creating a library of mutated glucose oxidase genes' or mutating glucose oxidases. Examiner respectfully disagrees. MPEP 2144 states that

> "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law." and
>
> "The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination."

"[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art

would reasonably be expected to draw there from." In the instant case, although the reference to not explicitly teach making mutated glucose oxidase genes, one skilled in the art would have reasonably led to conclude from the teachings of the cited references to prevent degradation of glucose oxidase in glucose sensors by using chemical agents or to make mutant glucose oxidases that are resistant to peroxide because methods of mutagenizing an enzyme to become resistant against a chemical is well known, as taught by Stemmer et al.

Applicants also argue that Examiner cites no suggestion or motivation in any of the cited reference for incubating mutated colonies of glucose oxidase with hydrogen peroxide and Valdes et al. teaches away from such methods, by instead, referring to conventional procedures (using additives for deactivating or destroying hydrogen peroxide) and thus teach away from such methods. Examiner respectfully disagrees. Valdes et al. does not teach away from the claimed method. Valdes et al. teaches that degradation of glucose oxidase can be addressed by preventing "the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph). Although the reference to not explicitly teach making mutated glucose oxidase genes, one skilled in the art would have recognized to prevent degradation of glucose oxidase in glucose sensors by using chemical agents or to use other "techniques", generating mutant glucose oxidases that are resistant to peroxide because methods of mutagenizing an enzyme to become resistant against a chemical is well known, as taught by Stemmer et al. Further, making and using mutant glucose oxidase that are resistant to hydrogen peroxide would eliminate the step of adding chemical agents,

which is advantageous for glucose sensors comprising said mutant glucose oxidase implanted in an organism.

Applicants also argue that there is no reasonable expectation of success since one of ordinary skill in the art would not have known gene mutation processes and known glucose oxidase purifying, isolating and measuring processes to modify Valdes et al. since Stemmer does not appear to mention glucose oxidase anywhere in its disclosure and Hatzinikolaou et al. fails to provide any motivation or suggest any relation to a gene mutation procedure or of addressing peroxide degradation of glucose oxidase. Similarly as argued above, the method taught by Stemmer can be applied to known genes (see claims of Stemmer). Glucose oxidase genes are well known in the art (Hatzinikolaou et al.). Further, obviousness does not require absolute predictability, but only a reasonable expectation of success. One of ordinary skill in the art would have had a reasonable expectation of success to practice the claimed invention since Hatzinikolaou et al. teaches glucose oxidase genes, Stemmer teaches a method of generating a library of mutant genes and screening for activity and other desired properties, such as resistance to a chemical, and Wagner teaches how to determine activity of glucose oxidase by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission.

Applicants argue that Examiner has failed to address the significant issue of why one skilled in the art would have been motivated to select a process as described by Stemmer, to make such a drastic change in the direction taken by those most skilled in the prior art as described by Valdes et al., which employees addition of additives.

Examiner respectfully disagrees. Valdes et al. dose not limit preventing degradation of glucose oxidase by only adding chemical agents, but teaches that degradation of glucose oxidase can be addressed by preventing "the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph). As discussed above, one having ordinary skill in the art would have recognized to apply other techniques, such as mutagenizing the enzyme, thus eliminating the root of the problem, eliminating an extra step of adding chemicals. One having ordinary skill in the art would have looked to mutating glucose genes that are resistant to hydrogen peroxide because Valdes et al. teaches that additives, such as catatalse, is inactivated by hydrogen peroxide, which would be limited in preventing degradation of glucose oxidase. The solution to preventing degradation of glucose oxidases mentioned by applicants (Heller et al. and Yin et al.) are all drawn to somehow neutralizing the effects of hydrogen peroxide. But since Stemmer teaches a method of making an enzyme having an advantageous predetermined property, such as to a chemical, one having ordinary skill in the art would have recognized to solve the problem of glucose oxidase degradation by peroxide by making glucose oxidase mutants that are resistant to hydrogen peroxide.

Applicants also argue that one of ordinary skill in the art would not have found Valdes et al's discussion of the degradation of glucose oxidase a suggestion to employ a mutation process as described in the Current Protocols in Molecular Biology. Current Protocols in Molecular Biology was not used in this rejection.

Applicants also argue that motivation to combine or statements of motivation derived from applicant's own specification are not sufficient to set forth a *prima facie*

case of obvious. Examiner respectfully disagrees. It appears that applicant's are arguing that the examiner's conclusion of obviousness is based upon improper hindsight reasoning derived from applicant's specification. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, prior art teaches that glucose oxidase is degraded by hydrogen peroxide (Valdes et al.) and teaches that this problem can be addressed by preventing degradation of the enzyme. Stemmer teaches a method of making mutant enzymes enzyme having an advantageous predetermined property, such as resistance to a chemical, knowledge which was within the level of ordinary skill. Therefore, the motivation to combine the cited reference are not derived from applicant's own specification, but the motivation comes from the combined teachings of the cited references.

Hence the rejection is maintained.

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Yong D. Pak
Patent Examiner 1652

Tekchand Saidha
Primary Patent Examiner 1652